REMARKS

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Applicants' representative wishes to thank Examiners Qian and Yucel for extending the courtesy of a telephone interview on March 25, 2003, and for the helpful discussion that ensued.

Status of the claims

Claims 1-64 were pending in the present application. Applicants previously elected Group I, claims 1-20 and 33-39, canceled claims 2, 13, and 34, and added new claims 65-92. By this response, claims 1, 4, 12, 15, and 33 have been amended, claims 5, 11, 16, and 20 have been canceled, and new claims 93-97 have been added. Therefore, claims 1, 3, 4, 6-10, 12, 14-19, 33, 35-39, and 65-97 are currently under consideration.

Claims 12, 15, and 33 have been amended to remove multiple recitations of the designations (a) and (b) for clarification purposes. The other amendments to the claims are supported by the specification as follows: Support for the amendments to claims 1, 4, 12, and 33 may be found, for example, on page 21, lines 9-10. Support for the amendment to claim 15 may be found, for example, on page 23, lines 10-11. No new matter has been added.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with Markings to Show Changes Made**."

With respect to any claim amendments or cancellations, Applicants have not dedicated to the public or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants note that the initial amendments to the claims filed in a Preliminary Amendment on September 13, 2002 were not made in response to any rejection, since no rejections were on the record at that time. The amendments were made to expedite prosecution in light of business needs.

Information Disclosure Statement

Applicants respectfully note that the Examiner has initialed and returned the Form PTO-1449s that were submitted with the Supplemental Information Disclosure Statements filed on November 7, 2001, February 27, 2002, and September 13, 2002. However, as discussed during the telephone interview, the Examiner has not initialed the Form PTO-1449 submitted with the Information Disclosure Statement filed on September 18, 2001. In a subsequent voice mail to Applicants' representative, the Examiner indicated that she was unable to locate the September 18, 2001 Information Disclosure Statement at the Patent Office. Therefore, Applicants are resubmitting this Information Disclosure Statement under separate cover by hand delivery. Applicants would appreciate the Examiner initialing and returning the form, indicating that the references submitted on September 18, 2001 have been considered and made of record.

A further Supplemental Information Disclosure Statement is submitted herewith. Applicants would appreciate the Examiner initialing and returning the Form PTO-1449 for this Information Disclosure Statement as well.

Drawings

The drawings are objected to in view of informalities indicated by the Draftsperson on PTO form 948. In response to this objection, formal drawings are submitted herewith.

Claim Objections

Claims 3 and 14 are objected to under 37 CFR §1.75(c), as allegedly of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants respectfully traverse this objection.

The Examiner states that claims 3 and 14, which recite "wherein the polynucleotides are double stranded DNA," do not further limit parent claims 1 and 12, which recite "wherein the dsDNA epitopes are polynucleotides." As discussed during the interview, "polynucleotide," as recited in claims 1 and 12, refers to the dsDNA epitope. The term "polynucleotide" is defined on pages 14 and 15 of the specification as including "double-stranded DNA" in addition to a number of other polynucleotide species, such as single-stranded DNA, triple-stranded DNA, RNA, DNA-RNA hybrid, etc. Thus, recitation of "dsDNA" in claims 3 and 14 further limits the claims to this particular species of "polynucleotide," and thus further limits parent claims 1 and 12.

During the interview, the Examiners suggested that claim 1 be amended to move the phrase "wherein the dsDNA epitopes are polynucleotides" to a position directly after the recitation of "two or more molecules comprising double stranded DNA (dsDNA) epitopes," to more clearly convey that "polynucleotides" refers to the dsDNA epitopes that bind to anti-dsDNA antibodies in the individual. In accordance with the Examiners' suggestion, claim 1 has been so amended, solely to clarify the claim.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the objection under 37 CFR §1.75(c).

Rejections under 35 U.S.C. §112, first paragraph

Claims 1, 3, 33, 35-39, 65-72 and 90-92 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the

time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

As a preliminary matter, Applicants respectfully note that the claims recite that "the dsDNA epitopes are *polynucleotides*," which is fully supported throughout the specification. (See, for example, page 21, lines 8-16.) As discussed above, the claims have been amended, in accordance with the Examiners' suggestion during the telephone interview, to move the phrase "wherein the dsDNA epitopes are polynucleotides" into closer proximity with the first recitation of "dsDNA epitopes" in the claim, to more clearly convey that "polynucleotides" refers to the dsDNA epitopes.

The Examiner states that the phrase "two or more molecules comprising double stranded DNA epitopes" is not supported by the specification because no molecules other than dsDNA are disclosed as dsDNA epitopes. Applicants respectfully submit that the specification discloses that "[d]ouble-stranded DNA (dsDNA) epitopes for use in the conjugates of the present invention may be *any chemical moiety* which specifically binds to a dsDNA antibody" (page 30, lines 25-26, emphasis added), including polynucleotides, as currently claimed (page 30, lines 29-30). The specification also states that double stranded DNA epitopes include molecules which comprise such epitopes, as presently claimed. Page 13, lines 16-18. Double stranded DNA epitopes are disclosed as including mimetics of naturally-occurring double-stranded DNA that share an epitope, or binding specificity with double-stranded DNA, including "any chemical substance which exhibits the requisite binding properties," such as organic or inorganic molecules, polypeptides, polynucleotides, carbohydrates, lipids, lipopolysaccharides, lipoproteins, etc. Page 16, lines 9-16. Thus, the specification discloses molecules other than dsDNA which are dsDNA epitopes.

The Examiner further states that the specification fails to describe the characteristic or structure that the claimed molecules must share. As discussed above, "dsDNA epitope" is defined in the specification as including "any chemical moiety which exhibits *specific binding to an anti-double-stranded DNA antibody*." Page 13, lines 16-18, emphasis added. Thus, the

claimed dsDNA epitopes all share the common characteristic of *specific binding* to anti-dsDNA antibodies. The MPEP describes identifying characteristics that may provide sufficient written description for biomolecules as including "binding specificity" and "antibody cross-reactivity." MPEP §2163(II)(A)(3)(a). Thus, the presently-claimed dsDNA epitopes are sufficiently described in the specification in terms of their common identifying characteristics of *binding specificity* to an anti-dsDNA antibody (page 13, lines 16-18). All of the claimed molecules comprising a dsDNA epitope must share this common feature by definition, and the specification adequately describes this characteristic. Further, as discussed above, all of the claims recite that the dsDNA epitopes are *polynucleotides*. The claimed polynucleotides share the common feature of specific binding to an anti-dsDNA antibody.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Claims 1, 3, 4, 8, 9, 10, 12, 14, 15, 19 and 65-89 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Applicants respectfully traverse this rejection.

The Examiner states that the specification teaches that patients with K_D' greater than 0.8 do not respond to LJP394 effectively and that one of skill in the art would have to engage in undue experimentation to practice the claimed methods. Applicants disagree and respectfully note that Figure 10 shows that some reduction in anti-dsDNA antibody levels was obtained for a patient population with low affinity antibodies (K_D' greater than 0.8 mg/ml) treated at a dose of 100 mg LJP394 per week (see page 53, line 31 - page 54, line 4). Thus, K_D' of 0.8 is not an absolute cutoff with respect to the effectiveness of the claimed methods. However, solely to expedite prosecution, claims 4 and 15 have been amended to recite a K_D' of less than about 0.8, rendering this rejection moot.

With respect to claims 1 and 12, the Examiners indicated during the telephone interview that it would be acceptable to not recite a K_D' in these claims in view of the claim structure. The specification is enabling for using affinity as a basis for selection of an individual to receive treatment, as recited in claims 1 and 12. Methods for measuring antibody affinity are well known in the art, and several of such methods are described in the specification, for example on page 29, line 20 - page 30, line 8. Thus, one of skill in the art would readily understand how to make and use the invention claimed in claims 1 and 12, and their associated dependent claims.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1, 3, 10, 12, 14, 33, 35-39, 76-82, and 90-92 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite due to recitation of the phrase "wherein the dsDNA epitopes are polynucleotides." Applicants respectfully traverse this rejection.

The Examiner states that it appears to be redundant to recite that dsDNAs are polynucleotides. As discussed during the interview, the claims recite that dsDNA *epitopes* are polynucleotides, *not* that dsDNAs are polynucleotides. One of skill in the art would readily understand that the epitopes recognized by antibodies that bind dsDNAs may be polynucleotides (see, for example, page 30, lines 25-30). Thus, the claims are clear as written.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Claims 4-9, 11, 15-20, 33-39, 73-75, and 83-92 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite due to recitation of the term "about." Applicants respectfully traverse this rejection.

The Examiner states that recitation of "about 1.0 mg" or "about 0.8" renders the claims indefinite because the value of K_D' is unclear. Applicants respectfully submit that the use of the

term "about" does not render claims using this term indefinite. It is well established that the use of a relative term does not render a claim indefinite under 35 U.S.C. §112, second paragraph. *See Seattle Box Co. v. Industrial Crating & Packaging, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984) (stating that the fact that the claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite); *see also* U.S. Patent & Trademark Office, Manual of Patent Examining Procedure §2173.05(b). Claims are definite where "the claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits. As a matter of law, no court can demand more." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94, 95 (Fed. Cir. 1986) (holding that the limitation "at least about 10^8 liters per mole," when used to describe antibody affinity, was definite in view of the specification and the inexact nature of the subject matter).

The term "about" is accepted and widely used in patent practice and is clearly acceptable under the law. The word "about" does not have a universal meaning in patent claims; rather, its meaning depends on the technological facts of the particular case. *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217-18 (Fed. Cir. 1995). "About" is neither broad nor arbitrary, but rather serves as a flexible term with a meaning similar to "approximately." *Conopco, Inc. v. May Dep't Stores Co.*, 46 F.3d 1556, 1561 (Fed. Cir. 1994).

Applicants wish to draw the Examiner's attention to *Hybritech, Inc. v. Abbot Laboratories*, 849 F.2d 1446 (Fed. Cir. 1988), in which the Federal Circuit considered claims that recited antibody affinity as "at least about 10^8 liters/mole" and upheld an interpretation of this claim language as encompassing a *range of antibody affinities* on the basis that measurement errors are inherent in antibody affinity determinations. The term "about" is also used in the context of antibody affinity in the present claims. Extending the holding in *Hybritech* to the current claims, description of antibody affinity using the word "about" is appropriate in view of the disclosed subject matter, the specification, and the cited case law, and is acceptable under the law.

In a search of patents issued in the last twelve months, Applicants' representative found six patents with claims that use the term "about" in the context of antibody affinity. (See U.S. Patent Nos. 6,375,680, 6,512,097, 6,399,066, 6,538,114, 6,534,633, and 6,524,866.) The fact that the Patent Office has previously issued these types of claims further indicates that the term "about" is not indefinite when used to describe antibody affinity.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Claims 33, 35-39, and 90-92 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite due to recitation of two (a)s and two (b)s in claim 33. Claim 33 has been amended to replace one set of (a) and (b) designations with the designations (i) and (ii), thereby obviating the rejection. Claims 12 and 15, which also recited two (a)s and two (b)s, have been amended in the same way.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Claims 1, 3-12, 14, 33, 35-39, and 65-92 are rejected under 35 U.S.C. §112, second paragraph, as allegedly incomplete due to omission of essential steps, such omission allegedly amounting to a gap between the steps.

Applicants traverse the rejection and respectfully maintain that the claims as written interrelate the elements of selecting an individual to receive treatment for SLE on the basis of affinity of the individual's antibodies for a dsDNA epitope and administering a conjugate comprising the dsDNA epitope to an individual so selected for treatment. Thus, Applicants have not omitted "essential steps" and the claims are clear as written.

During the telephone interview, the Examiners suggested that addition of language to the claim to clarify what the treatment entails would obviate the rejection. Thus, in accordance with the Examiners' suggestion and solely to expedite prosecution, claims 1, 4, and 33 have been

amended to recite "wherein said treatment comprises administering said conjugate to the individual." Claim 12 has been amended to clarify that treatment involves administering the conjugate to a selected individual. These are cosmetic, non-narrowing amendments using the Examiner's preferred language.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §102(b)

Claims 1, 3, 10, 12, 14, 66-68, 69-72 and 77-82 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Jones et al. (1995) *J. Med. Chem.* 38:2138-44. Applicants respectfully traverse this rejection.

In order to anticipate, a reference must teach each and every element of a rejected claim. As discussed during the interview, Jones et al. do not teach use of affinity of antibodies from an individual as a basis or tool for selection of an individual to receive or continue to receive treatment, as presently claimed. Thus, this reference does not anticipate the claimed invention. The Examiner herself states that "*[t]he art is silent* on said method of treating SLE by measuring initial antibody-dsDNA affinity." (Office Action, page 4, emphasis added.)

Jones et al. teach synthesis and characterization of a conjugate which includes four double-stranded oligonucleotides attached to a nonimmunogenic valency platform molecule. This conjugate was administered to mice that had been pre-immunized with a KLH-dsDNA conjugate and was shown to significantly reduce the number of anti-double stranded oligonucleotide antibody-forming cells in a dose-dependent manner and render the mice unresponsive (tolerant) to further challenge with an immunogenic form of the oligonucleotide. *Affinity was not used as a basis for selecting which mice received treatment, nor did Jones et al. teach that affinity should be a criterion for selection.*

The Examiner states that since a Farr assay was used in Jones et al. to determine the specificity of antibodies in the pre-immunized mice, "this indicates the affinity of the antibodies

to the conjugate." Office Action, page 7. In Jones et al., binding was tested at a single antigen concentration, and the antibodies were only shown to be of "high enough" affinity to give a positive binding result. Thus, the antibodies were merely shown to be capable of binding dsDNA. Jones et al. do not teach use of an antibody affinity value as a basis for selection in a treatment protocol.

In conclusion, Jones et al. do not teach use of antibody affinity for an anti-dsDNA epitope as a *basis for selection* of individuals to receive or continue to receive treatment. Thus, Jones et al. do not anticipate the claimed invention.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b).

CONCLUSION

Applicants have, by way of the amendments and remarks presented herein, made a sincere effort to remove the issues for the rejections and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of the application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 252312007400. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: April 17, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 1, 4, 12, 15, and 33 have been amended as follows:

1. (Twice Amended) A method of treating systemic lupus erythematosus (SLE) in an individual, comprising administering to the individual a conjugate comprising (a) a non-immunogenic valency platform molecule and (b) two or more molecules comprising double stranded DNA (dsDNA) epitopes, wherein the dsDNA epitopes are polynucleotides which specifically bind to an antibody from the individual which specifically binds to double stranded DNA, ~~wherein the dsDNA epitopes are polynucleotides,~~ wherein affinity of the polynucleotides for the antibody from the individual is used as a basis for selecting the individual to receive or continue to receive the treatment, and wherein said treatment comprises administering said conjugate to the individual.

4. (Thrice Amended) A method of treating SLE in an individual, comprising administering to the individual a conjugate comprising (a) a non-immunogenic valency platform molecule and (b) two or more polynucleotides which specifically bind to an antibody from the individual which specifically binds to double stranded DNA, said polynucleotides consisting essentially of the sequence 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1), wherein the apparent equilibrium dissociation constant (K_D') for the polynucleotides with respect to the antibody from the individual before or upon initiation of treatment is less than about 0.8~~1.0~~ mg IgG per ml, ~~and~~ wherein said K_D' value or a functional equivalent thereof is used as a basis for selecting the individual to receive the treatment, and wherein said treatment comprises administering said conjugate to the individual.

12. (Twice Amended) A method of treating SLE in an individual comprising:

(a) assessing affinity of an anti-double stranded DNA antibody from the individual with respect to a dsDNA epitope which is to be used in treatment, wherein the individual is selected for treatment based on said antibody affinity; and

(b) treating said selected individual by administering to said selected individual a conjugate comprising ~~(a)~~ (i) a non-immunogenic valency platform molecule and ~~(b)~~ (ii) two or more of the dsDNA epitopes, wherein the dsDNA epitopes are polynucleotides which specifically bind to an antibody from the individual which specifically binds to double stranded DNA.

15. (Thrice Amended) A method of treating SLE in an individual, comprising

(a) assessing before initiation of treatment an apparent equilibrium dissociation constant (K_D') or a functional equivalent thereof for a polynucleotide in a conjugate and an antibody from the individual which specifically binds to double stranded DNA, said conjugate comprising ~~(a)~~ (i) a non-immunogenic valency platform molecule and ~~(b)~~ (ii) two or more polynucleotides which specifically bind to an antibody from the individual which specifically binds to double stranded DNA, said polynucleotides consisting essentially of the sequence 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1), wherein the individual is selected to receive the treatment if the K_D' is less than about 0.8~~1.0~~ mg IgG per ml; and

(b) administering to the individual the conjugate in an amount sufficient to increase the K_D'.

33. (Twice Amended) A method of treating SLE in an individual, comprising:

(a) assessing before or upon initiation of treatment an apparent equilibrium dissociation constant (K_D') for a dsDNA epitope in or a conjugate and an antibody from the individual which specifically binds to double stranded DNA, said conjugate comprising ~~(a)~~ (i) a non-immunogenic valency platform molecule and ~~(b)~~ (ii) two or more molecules comprising said

epitopes, wherein the said epitopes are polynucleotides which specifically bind to an antibody from the individual which specifically binds to double stranded DNA and

(b) administering to the individual the conjugate in an amount sufficient to increase the K_D', wherein treatment is continued if K_D' is increased at least about 20% compared to K_D' before or upon initiation of treatment, and wherein said treatment comprises administration of said conjugate to the individual.

Claims 5, 11, 16, and 20 are canceled.

Claims 93-97 are new.